UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,229	12/20/2001	George Jackowski	2132.113	3487

21917 7590 01/16/2007

MCHALE & SLAVIN, P.A.
2855 PGA BLVD
PALM BEACH GARDENS, FL 33410

EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/032,229	JACKOWSKI ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-12 and 15-17* is/are pending in the application.

4a) Of the above claim(s) *5-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Claims 1-4 have been canceled and new claims 15-17 added as requested in the amendment filed on July 10, 2006. Following the amendment, claims 5-12 and 15-17 are pending in the instant application.

2. Claims 5-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 27, 2005.

3. Claims **15-17** are under examination in the instant office action. It is noted that claims 15-17 find their basis in and replace canceled claims 1-4.

4. The Examiner of U.S. Patent Application No. 10/032,229 has changed. In order to expedite the correlation of papers with the application, please direct all future correspondence to Examiner Ballard, Technology Center 1600, Art Unit 1649.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Claim Rejections

6. The rejection of claims 1-4 under 35 USC § 112, first paragraph (written description), as set forth at ¶ 7 of the previous office action (01/04/2006), is rendered moot in view of applicant's cancellation of said claims. As far as the rejection may apply to new claims 15-17, it is withdrawn in view of the current claim language.

7. The rejection of claims 1-4 under 35 USC § 112, second paragraph, as set forth at ¶ 9 of the previous office action (01/04/2006), is rendered moot in view of applicant's cancellation of said claims. As far as the rejection may apply to new claims 15-17, it is withdrawn in view of the current claim language.

8. The rejection of claims 1-4 under 35 USC § 103(a), as set forth at ¶ 13 of the previous office action (01/04/2006), is rendered moot in view of applicant's cancellation of said claims. As far as the rejection may apply to new claims 15-17, upon further consideration it is withdrawn.

Maintained and New Claim Rejections, Necessitated by Amendment

Claim Rejections - 35 USC § 112, first paragraph

9. The rejection of claims 1-4 under 35 USC § 112, first paragraph, as set forth at ¶ 6 of the previous office action (01/04/2006) is maintained for reasons of record insofar as it is applied to new claims 15-17, which replace canceled claims 1-4. Claims 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while

being enabling for detection of thrombospondin, does not reasonably provide enablement for diagnosis of Alzheimer's dementia via detection of a thrombospondin polypeptide in a body fluid sample from a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Newly added claims 15-17 are broadly drawn to a method for diagnosing Alzheimer's dementia in a mammal, determining a presence of a thrombospondin polypeptide in a body fluid sample from said mammal by contacting the sample with at least one antibody which specifically binds to a thrombospondin polypeptide weighing about 180 kDa, wherein the presence of said thrombospondin polypeptide is diagnostic for Alzheimer's dementia.

At page 10 of the response filed July 10, 2006, Applicants argue that Figures 1 and 2 of the instant specification provide data evidencing that a thrombospondin polypeptide weighing about 180 kDa was identified in samples obtained from patients with Alzheimer's disease but not in samples obtained from age-matched controls. Applicants thus assert that the 180 kDa thrombospondin polypeptide is shown to be a marker of Alzheimer's dementia and further assert that the instant specification fully enables a method of diagnosing Alzheimer's dementia by determining the presence of a thrombospondin polypeptide weighing about 180 kDa in a sample.

Applicants' arguments have been fully considered, but they are not deemed to be persuasive. The description of Figure 2 (p. 21 in the instant specification states that the 180 kDa band for thrombospondin is "not visible in 11 of the 15 age-matched controls.

From Fig. 2 it can be seen that all 13 AD samples show positive, 11 of the normals show negative, 4 of the age-matched controls show negative with possible dementia." However, this description does not match what is shown in Figure 2. The Examiner notes that there are nine (9) "normal" controls samples (designated with an "N") and eighteen (18) Alzheimer's disease (designated with "AD") samples shown in Figure 2, wherein three of the AD samples (ADH39, ADC003, and ADC005) are negative for the 180 kDa band. Thus, there are at least four cases in which individuals with possible dementia tested negative and three cases in which patients *already diagnosed with Alzheimer's disease* also tested negative for the thrombospondin polypeptide weighing about 180 kDa. Therefore, contrary to Applicants' assertions, based on the description for Figure 2 and Figure 2 itself, it clear that thrombospondin is not a specific marker for diagnosing Alzheimer's dementia because there is not an accurate correlation between the disease and presence of the polypeptide. Even the instant specification notes at page 11 that "[a]ny individual marker needs to be assessed by sensitivity, specificity, reliability and validity for the type of clinical situation to which it is meant to apply." Because of the inconsistency of the instant data, the claimed invention of diagnosing AD via detection of a thrombospondin polypeptide of ~180 kDa appears to be neither reliable nor valid.

Further, as stated previously, while thrombospondin is recognized as being present in Alzheimer's plaque pathology (see, in particular, Buée et al. *Amer J Pathol.* 1992; **141**(4): 783-788; cited on IDS), such is not diagnostic to dementia. Moreover, thrombospondin is noted to be detected in biological mammalian fluids not associated

with dementia (see, for example, Clezardin et al. *J. Chromatography*, 1984; **296**: 249-256, and Lawler et al. *Blood*, 1986; **67**(2): 555-558; both cited in previous office action). More recently, Sezaki et al. (*Exp. Biol. Med.* 2005; **230**: 621-630) report that thrombospondin-1 (TSP-1) is induced in rat myocardium following myocardial infarction, and TSP-1 induction is accelerated during ischemia/reperfusion. For example, Figure 3 demonstrates that a strongly positive TSP-1 protein signal, which is noted as a band at about 180 kDa, is apparent at 24 hours post-infarction. As aged individuals are at a higher risk for strokes and myocardial infarctions, it follows that there may be a greater likelihood of testing positive for thrombospondin but falsely positive for diagnosis of Alzheimer's dementia. Accordingly, this raises the issue that detection of thrombospondin in blood or other body fluid is not definitive of Alzheimer's dementia, giving rise to false positive diagnosis.

In summary, it would not be expected that one of ordinary skill in the art could successfully make and use the instant invention as broadly claimed for without undue experimentation. When combined with the complex nature of the invention, the unpredictability in the art regarding the diagnosis of Alzheimer's dementia, the breadth of the claims, and the lack of guidance or objective evidence from the instant specification demonstrating a strong correlation between the presence of a thrombospondin polypeptide and presence of AD, the claims merely represent an invitation to experiment to discover how to use Applicants' invention.

Claim Rejections - 35 USC § 112, second paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Newly presented claim 15 recites the phrase "a thrombospondin polypeptide weighing about 180 kDa", which is indefinite because the claim does not specify the manner in which the molecular weight was determined (native PAGE, denaturing SDS-PAGE, predicted from sequence, etc.) It is well known in molecular biology that the value of the molecular weight for a given protein depends entirely upon the manner in which it is determined. Therefore, the recitation of the molecular weight in the claim is not meaningful, as the metes and bounds of the claim cannot be ascertained.

12. Claims 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for being dependent from indefinite rejected claim 15.

Claim Rejections - 35 USC § 102

13. The rejection of claims 1-4 under 35 USC § 102(e), as set forth at ¶ 11 of the previous office action (01/04/2006) is maintained for reasons of record insofar as it is applied to new claims 15-17, which replace canceled claims 1-4. Newly added claims 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,605,592

to Ni et al. or in the alternative US PGPub 20020068319 by Ni et al., as evidenced by Asakura et al. (*J. Neuroimmunol.* 1996; **65**:11-19). The Ni et al. references are cumulative and are therefore cited together with identical reasoning therefore.

At page 18 of the response filed July 10, 2006, Applicants assert that Ni et al. does not teach a thrombospondin peptide, but a peptide that shares some similar domains with thrombospondin. Applicants further argue that even if Ni et al. did disclose thrombospondin, they do not teach a polypeptide subunit of thrombospondin-1 weighing about 180 kDa that was identified as present in Alzheimer's patients and absent in control patients and thus useful as a marker for diagnosing Alzheimer's disease. Applicants thus assert that Ni et al. cannot be said to either expressly or inherently describe each and every element in the claims as now presented for examination.

Applicants' arguments have been fully considered, but they are not deemed to be persuasive. As Applicants have duly noted, Ni et al. teach a novel THRAP protein that exhibits 13 thrombospondin-1 (TSP-1)-like domains, IgG-like domains and proteinase inhibitor-like domains, as in Figure 4. It is also noted that Figure 5 of the patent shows the regions of identity between the amino acid sequence of THRAP and the translation product of thrombospondin-like protein as determined by BLAST analysis. Further, Ni et al. disclose that the predicted molecular weight of the THRAP protein is about 191 kDa (see column 24, lines 46-47), which is "about 180 kDa" as instantly recited. Thus, the THRAP protein disclosed by Ni et al. bears striking homology to TSP-1, both in terms of its amino acid sequence and it predicted weight, and would thus meet the

limitation of "*a* thrombospondin polypeptide weighing *about* 180 kDa." Furthermore, the claims do not specify the manner in which the molecular weight was determined (native PAGE, denaturing SDS-PAGE, predicted from sequence, etc.) It is well known in molecular biology that the value of the molecular weight for a given protein depends entirely upon the manner in which it is determined. Therefore, the recitation of the molecular weight in the claims is not meaningful, and Ni fully anticipates this limitation.

Moreover, Ni et al. teach an analysis of the THRAP amino acid sequence (Figure 6), with highly antigenic regions of the THRAP protein identified, i.e., regions from which epitope-bearing peptides of the invention can be obtained. New claims 15-17 recite a method for diagnosing Alzheimer's dementia comprising contacting a sample of a body fluid with at least one antibody which specifically binds to a thrombospondin polypeptide weighing about 180 kDa and determining the presence of said thrombospondin polypeptide in said sample. The diagnostic method thus hinges on the specificity of the antibody for binding to a thrombospondin polypeptide in order to detect the polypeptide's presence. Because of the tremendous overlap in amino acid sequence and antigenic epitopes between the THRAP protein disclosed by Ni and the thrombospondin protein, it would be expected that the antibodies disclosed by Ni for detection of THRAP protein and diagnosis of Alzheimer's disease would be capable of detecting thrombospondin and diagnosing Alzheimer's dementia as instantly claimed. Antibodies, even monoclonal antibodies, are notoriously promiscuous in terms of their capacity to bind similar epitopes on different proteins. See, for example, Asakura et al., which evidence that a monoclonal antibody (designated SCH94.03) was capable of

specifically recognizing five different proteins: rat kinesin light chain, mouse thrombospondin-1, mouse oncofetal antigen, RNA polymerase beta subunit, and nuclear phosphoprotein (see abstract).

Finally, as noted in the previous office action, Ni et al. teach that the protein may be detected in bodily fluids such as lymph, serum, plasma, urine, synovial fluid and spinal fluid, taken from an individual having the disorder and compared to a sample from an individual not having the disorder. Additionally, Ni et al. disclose various immunoassay techniques for detecting a polypeptide of the invention, including, but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassay, ELISA, "sandwich" immunoassays, western blots, precipitation reactions, etc. (see column 186, lines 45-67). Ni et al. teach that detection of THRAP polypeptide and/or fragments thereof in a biological sample is useful for the diagnosis of Alzheimer's disease (see column 91, lines 27-37). Accordingly, the teachings of Ni et al. anticipate instant claims 15-17.

Conclusion

14. No claims are allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Kimberly Ballard, Ph.D.
January 5, 2007

ELIZABETH KEMMERER
PRIMARY EXAMINER